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LETTERS TO THE EDITOR

Cyclooxygenase-2 in Myocardial Ischemia: Is It Really a Friend?

We read with interest the elegant experimental study performed by Shinmura et al. (1) and published in the *Journal* showing that cyclooxygenase-2 (COX-2) inhibition prevents delayed ischemic preconditioning and, in particular, reduction in postischemic stunning. However, we believe it is unlikely that their experimental findings have relevant clinical implications, as repeatedly suggested by the investigators. Ischemic preconditioning has been shown to reduce infarct size and myocardial stunning. However, the assessment of infarct size is probably more complex than believed a few years ago. Indeed, the majority of myocardiocytes are lost through apoptosis (2,3), which is not assessed by standard techniques, rather than through necrosis as previously thought. Therefore, if assessment of infarct size is based solely on enzyme leakage and/or on the extent of necrosis and fibrosis at pathology it does not reflect total effective myocardiocyte loss. Notably, classic studies on the effects of preconditioning on infarct size did not take into account cell apoptosis, which might even be enhanced by early or late ischemic preconditioning (2,4). Moreover, ischemic preconditioning-induced reduction in stunning does not necessarily have to be considered beneficial. The ischemic cell undergoes both short- and long-term modifications to confront hypoxia, in a delicate balance between survival and death (5,6). Stunning and hibernation are natural responses to ischemia and are probably part of the cellular mechanisms of adaptation aimed toward programmed cell survival after ischemia (5,6), whereas prolonged ischemia (either with or without reperfusion) causes cell death.

Finally, and most importantly, recent data indicate that COX-2 is a mediator of ischemic damage. Takadera et al. (7) have shown that COX-2 plays a key role in central nervous system apoptosis. We have recently found that COX-2 expression in recent myocardial infarction (MI) is associated with higher apoptotic rates (8); Saito et al. (9,10), using an experimental model of MI, have reported beneficial effects, in terms of postinfarction dysfunction, of COX-2 inhibitors, and just recently high-dose aspirin was found to protect myocardiocytes from apoptosis (11). Of note, in a different experimental setting, Zhang et al. (12) found an increase of COX-2 activity in genetically engineered animals prone to heart failure, and, most interestingly, they describe beneficial effects of selective COX-2 inhibition.

In conclusion, though COX-2 may provide a friendly protection to ischemic myocardiocytes, as suggested by Shinmura and colleagues (1), evidence is still too scant to scientifically discard its potential role as a foe leading to unfavorable outcomes in the process of cardiac adaptation to ischemia. The present study by Shinmura et al. (1) convincingly shows that COX-2 plays an active role in myocardial response to ischemia and that inhibition of COX-2 significantly affects the course of events after ischemic insults. Whether the effect of COX-2 is beneficial or deleterious in the clinical setting cannot be drawn from current data. Thus, the statement that COX-2 inhibitors should be used with caution because they may deprive the heart of its innate defensive response is completely speculative to date as further studies are needed, and COX-2 may ultimately be found to be more a "foe" than a "friend."

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REPLY

We welcome the chance to reply to the letter of Dr. Abbate and colleagues, as this gives us an opportunity to rectify a number of common misconceptions. First, the assertion by Dr. Abbate and colleagues that (following myocardial ischemia/reperfusion) "the majority of myocardiocytes are lost through apoptosis" is not supported by any evidence. Whereas apoptosis does occur after acute myocardial ischemia and reperfusion (1), the *quantitative* aspects of this process remain controversial and, at best, speculative. Regardless, measurements of infarct size at 72 h after reperfusion (as done by Shinmura et al. [2]) would include both necrotic and apoptotic cell death. It is also incorrect to state that

apoptosis might be enhanced by late preconditioning—again, no evidence exists to support this assertion. On the contrary, late preconditioning produces a marked reduction in infarct size (3). There is also no evidence to support the suggestion by Dr. Abbate and colleagues that reducing stunning is not beneficial; 20 years of research have shown that myocardial stunning is an unnecessary manifestation of reperfusion injury, which can be minimized without adverse consequences (4). The antistunning effects of late preconditioning (3) are associated with sustained improvement in left ventricular (LV) function (5).

Similarly, the statement by Dr. Abbate and colleagues that "COX-2 [cyclooxygenase-2] is a mediator of ischemic damage" is not supported by the available evidence. The study by Takadera et al. (6) dealt with PGE_2 (rather than COX-2 per se) and examined brain injury rather than cardiac injury. Apparently the abstract cited by Dr. Abbate and colleagues (which is not available at the time of this writing) showed an association between COX-2 expression and apoptosis; this association does not in any way indicate a cause-and-effect relationship. Saito et al. (7) assessed LV function (not infarct size) at four weeks after permanent occlusion (not after transient occlusion followed by reperfusion). Their study examined the role of COX-2 in LV remodeling, which is completely different from the role of COX-2 in limiting acute ischemia/reperfusion injury; the two issues should not be confused. The second study by Saito et al. (8) also examined a permanent coronary occlusion (without reperfusion) and did not measure infarct size as a percent of the risk region. Contrary to the statements by Dr. Abbate and colleagues, considerable evidence indicates that COX-2 by-products (particularly prostacyclin) exert antiapoptotic actions (9). The abstract by Iwai-Kanai et al. (10) examined apoptosis induced in vitro by isoproterenol or H_2O_2 (not by ischemia) in neonatal (not adult) cardiac myocytes. There is no evidence that aspirin acted by inhibiting COX-2 or that the model used in that study (10) has anything to do with myocardial ischemia/reperfusion. Although COX-2 has been reported to mediate apoptosis in Gh transgenic mice (11), this is not a setting relevant to myocardial ischemia/reperfusion injury, and the investigators indicated that the actions of COX-2 are complex (11).

In August 2000, we demonstrated, for the first time, that COX-2 is a cardioprotective protein that alleviates both myocardial stunning and infarction (2). We have subsequently reviewed the mounting evidence for a protective role of COX-2 (9). Three years have passed and increasing evidence supports our hypothesis. Cyclooxygenase-2 protects isolated myocytes from oxidative stress (12), and COX-2 inhibitors aggravate doxorubicin-mediated injury (13). Targeted disruption of the *COX-2* gene results in myocardial fibrosis (14). Myocardial ischemia/reperfusion injury is exacerbated in COX-2 null mice (15), implying that constitutively expressed COX-2 is cardioprotective. Moreover, PGI_2 is a potent cytoprotective prostanoid (9), and COX-2 has been found to be the major source of systemic biosynthesis of PGI_2 in healthy volunteers (16) and in patients with atherosclerosis (17).

As elaborated elsewhere (9), the concept that COX-2 is deleterious during acute myocardial ischemia is a common misconception. We propose that the biological effects of COX-2 may differ depending on the cellular type(s) where it is expressed (e.g., vascular wall vs. cardiac myocytes), the pathophysiological setting, and the ability of cells to metabolize COX-2-derived PGH_2 into cytoprotective prostanoids.

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